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# Clinical Trials and the FDA

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The biotechnology sector has emerged as one of the hottest of the past year. More and more investors are pouring their money into this sector, hoping that companies will translate flashy new technologies into revenue-producing drugs. While biotechnology has come of age, and the number of profitable companies with products on the market has continued to swell, the vast majority of companies are still pinning their hopes on the positive outcomes and subsequent FDA approval of the drugs being tested in clinical trials. This article is for those investors who are interested in learning a little more about the FDA and the clinical trial process.

The FDA, short for Food and Drug Administration, is the government agency responsible for ensuring the health and safety of consumers in the areas of drugs, biologics, food, cosmetic products, and medical devices. It is the agency's mission to ensure that these products are safe, effective, and are produced under sanitary conditions. In addition, all product packaging and labeling should be truthful, informative, and not deceptive in any way.

**The FDA: A Short History**
The FDA's roots date back to 1862, when Abraham Lincoln appointed chemist Charles M. Wetherill to serve in the newly created Department of Agriculture. Wetherill's appointment marked the beginning of the Bureau of Chemistry, later the Food and Drug Administration. In 1902, the Biologics Control Act was introduced, which authorized the Public Health Service to regulate and license biological drug laboratories in the production of antitoxins used in vaccines. The catalyst for this act was the death of 10 children after they received a vaccine shot. It was later discovered that the horse used in the production of the antitoxin was infected with tetanus.

In 1911, in response to the widespread sales of "snake venom" and other wonder cures, the Sherly Amendment was passed. This amendment made it a crime to make false claims in drug labeling.

In 1928, the government formed a separate law enforcement agency, originally called the Food, Drug, and Insecticide Administration. In 1930, the name was changed to the Food and Drug Administration.

The foundation of the modern clinical trial process was enacted in 1938 with the Federal Food, Drug, and Cosmetic Act. This was also the first attempt to regulate cosmetics and medical devices. This act required that drugs be proven safe prior to marketing. The manufacturers of drugs now had to provide scientific proof of safety by submitting an Investigational New Drug (IND) filing prior to human trials, and a New Drug Application (NDA) before marketing new drug products.

In 1962, the FDA was thrust into public view as a result of the discovery that the use of Thalidomide, a sleeping pill, resulted in thousands of birth defects in western Europe. Because of the FDA's role in

keeping the drug off the market in the U.S., the agency received a lot of positive press. Twenty years later, the much publicized deaths of seven people from Tylenol laced with cyanide prompted the passage of tamper-resistant packaging regulations by the FDA in 1982.

In 1983, the Orphan Drug Act provided incentives for drug companies to develop drugs for rare diseases.

Finally, in 1992, the Prescription Drug User Fee Act was passed, which required drug and biologic manufacturers to pay application and other fees to the agency. This revenue is used to hire more FDA reviewers, and has resulted in increased efficiency in the drug approval process.

**The Clinical Trial Process**

The drug approval process starts in the laboratory. After discovering a promising compound, studies using the compound in cell cultures, isolated tissues, and laboratory animals are conducted. This gives researchers a pretty good idea of what to expect in human trials. On average, only one compound in a thousand will actually make it to human testing. Assuming the data is promising, the company makes the decision whether to begin the long and costly process of getting the compound to market. Since most drug companies have multiple candidates, the company must take into account the size of the potential patient population, whether the market for that particular drug is already well-served, and the company's financial situation, all of which will factor in to the decision to begin clinical trials. Because most companies file for and receive patents for the commercial use of the compound that they are developing during pre-clinical trials, the patent clock usually starts ticking at this point. Patents generally last between 17 years for those dated before June 7, 1995, and 20 years for patents granted after that date. The pre-clinical trials for most drugs average about five years. Also, the patent protection for the drug, generally lasting 17 years, begins to tick once the compound begins pre-clinical trials. The pre-clinical trials for most drugs average about five years.

Assuming the company decides to pursue human studies, it must first submit an Investigational New Drug application to the FDA for approval. The IND becomes effective 30 days after receipt by the FDA (assuming the FDA does not require further information), and must be filed annually thereafter until the completion of clinical testing. The IND must provide pre-clinical data of sufficient quality to justify the testing of the drug in humans. About 85% of all IND applications move on to begin clinical trials. Assuming the company receives FDA go-ahead, the company will move the drug on to Phase 1 testing in human subjects. At this point, the compound has a one in five chance of eventually reaching the market, and will normally take another five to nine years to reach that destination.

**Phase 1**

Phase 1 trials concentrate on developing the drug's safety profile. The human subjects in the study are normally healthy volunteers, though sometimes patients who have terminal illnesses and have no other therapeutic alternative will take part in Phase 1 studies as well. The sample is normally not more than 100 patients in Phase 1. The basic goal of Phase 1 is to determine how the drug is absorbed, distributed in the body, metabolized, and excreted. The duration of the drug's effects are also measured. Phase 1 testing ranges from one to three years, on average.

Assuming the data from Phase 1 are positive and the safety of the compound is established, the drug moves on to Phase 2 testing. If the company moves on to begin Phase 2 trials, the drug's chance of eventually making it to market improves to just under 30%.

**Phase 2**

Phase 2 trials consist of small, well-controlled experiments to continue to evaluate the drug's safety

and assess side effects. The drugs are given to volunteers (usually between 100 and 300 patients) who actually suffer from the disease or condition being targeted by the drug. This phase is where the optimal dosage of the drug is established. Also, statistical end points are established for the drug that represent the targeted favorable outcome of the study. The current standard of care for the medical condition can be used as a benchmark in setting the end point. Phase 2 trials last an average of two years.

A drug that moves on to begin Phase 3 testing has about a 60% chance of actually being approved by the FDA.

**Phase 3**
Phase 3 testing is intended to verify the effectiveness of the drug against the condition that it targets, based on the statistical end points established in Phase 2. The study also continues to build the safety profile of the drug and record possible side effects and adverse reactions resulting from long-term use. Phase 3 studies are tightly controlled, double-blind studies with a sample size of at least 1000 patients. If the drug proves to be effective in this stage, the trial is deemed successful (pivotal). Normally two pivotal trials are required to ensure the validity of the studies, although if the results are extremely strong, one may suffice. Phase 3 testing averages between three and four years.

Assuming the drug reaches the desirable end point in Phase 3 trials, the company will then file a New Drug Application, which can contain 100,000 pages of data supporting the efficacy and safety of the drug. At this point, the drug has better than a 70% chance of being approved by the FDA.

Approval of the NDA can take anywhere from two months to an extreme of several years (in the case that the FDA requests additional information), with an average wait of between 18 and 24 months. Upon approval, the company may begin to market and distribute the drug.

**Phase 4**
Once the drug is on the market, the company must continue to perform observational studies in an ongoing evaluation of the drug's safety during routine use. The company also attempts to monitor any usage of the drug for conditions other than the approved medical indication. If the drug is being successfully used for off-label indications, the company will often initiate further clinical trials for those indications in order to widen the potential market for the drug. The company cannot advertise or endorse off-market use of the drug, however.

**For the Investor**
The clinical trial process is costly as well as time-consuming. Estimates as to the cost of pushing a drug through clinical trials range from between $350 million and $500 million. Investors interested in early stage companies should factor in the costs, risk, and extended time to market required for FDA approval.

Investors interested in the biotechnology sector would do well to consider companies that already have one or more successful products on the market, have a large pipeline of candidate drugs, and have plenty of cash to fund the development of their new drug candidates. **Amgen** (Nasdaq: AMGN), **Biogen** (Nasdaq: BGEN), **Chiron** (Nasdaq: CHIR), and **Genentech** (NYSE: DNA), **Immunex** (Nasdaq: IMNX), and **MedImmune** (Nasdaq: MEDI) are some of the largest companies in the biotech sector. You can find their drug pipeline information at the following links:

- Amgen's Pipeline
- Biogen's Pipeline

- Chiron's Pipeline
- Genentech's Pipeline
- Immunex's Pipeline
- MedImmune's Pipeline

Zeke Ashton found *The Fundamentals of Clinical Research*, published by The Association of Clinical Research Professionals, and the April 2000 issue of *Scientific American* helpful in writing this article.



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